An analytical model for a thick-walled alveolus undergoing large deformation reveals a skewed collagen fiber waviness distribution as key to inflation stability with implications on alveolar pressure and stress

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Introduction

- While alveolar surfactant has extensively been modeled in relation to protecting the alveoli against collapse (i.e. deflation stability), the quantitative investigation of how healthy alveoli are protected against over-distension (i.e. inflation stability) is not fully under stood.
- ➤ **We hypothesized that the process of recruiting elastic wavy collagen fibers during inflation is a mechanism that can provide inflation stability to the alveolus.**
- To this end, we developed an analytical model of a thick-walled alveolus with an adjustable collagen waviness distribution in order to investigate the role of fiber waviness in (1) inflation stability, and (2) the shape of the macroscopic pressure-volume (P-V) relationship of alveolar tissue.

Methods

Model Description

- The alveolus is assumed to be a homogeneous and isotropic thick-walled sphere.
- Elastin and wavy collagen fibers are embedded within its thickness.
- At rest, the inner and outer radii are R_i and R_e respectively ($R_i \leq R \leq R_e$).
- As the alveolus expands, the wavy fibers are gradually straightened and recruited to bear stress.
- The parameters w_2, w_1, Y_{ec}, α, and β represent the maximum and minimum collagen waviness (w), effective fiber stiffness (fiber area fraction x stiffness), and the two beta distribution shape parameters, respectively.
- As the alveolus is inflated by a stretch ratio λ, the collagen fibers are recruited, and their contribution to the alveolar wall circumferential true stress (σ_c) is:

$$\sigma_c(\lambda, R) = \frac{\delta_c Y_{ec}}{B(\alpha,\beta)\alpha(\alpha+1)}\frac{R_i}{R}\lambda\frac{\lambda-w_1}{w_1}\left(\frac{\lambda-w_1}{w_2-w_1}\right)^{\alpha}((\alpha+1)A_1 - \alpha B_1) \quad (1)$$

$$A_1 = F_1\left(\alpha; 1-\beta, 1; \alpha+1; \frac{\lambda-w_1}{w_2-w_1}, -\frac{\lambda-w_1}{w_1}\right) \quad (2)$$

$$B_1 = F_1\left(\alpha+1; 1-\beta, 1; \alpha+2; \frac{\lambda-w_1}{w_2-w_1}, -\frac{\lambda-w_1}{w_1}\right) \quad (3)$$

where F_1 is the Appell Hypergeometric Function of two variables.

- The elastin fibers with effective stiffness Y_{ee} contribute to the circumferential stress according to:

$$\sigma_e(\lambda, R) = \delta_e Y_e \frac{R_i}{R}\lambda(\lambda-1) \quad (4)$$

- For a thin-sphere, the combination of these stresses at the middle layer balances the alveolar pressure P_{alv} as a function of the inner stretch ratio (λ_i) thus:

$$P_{alv}(\lambda_i) \cong 2\left[\sigma_c\left(\lambda_i, \frac{R_e+R_i}{2}\right) + \sigma_e\left(\lambda_i, \frac{R_e+R_i}{2}\right)\right] \quad (5)$$

Model Data Fitting & Simulations

- The model was fit to the P-V relationship from a human and to force-length data from alveolar tissue strips (Fig. 1). We evaluated fiber stresses (Fig. 2), alveolar stresses (Fig. 3), key factors for inflation stability (Fig. 4), and P-V sensitivity to the model parameters (Fig. 5).
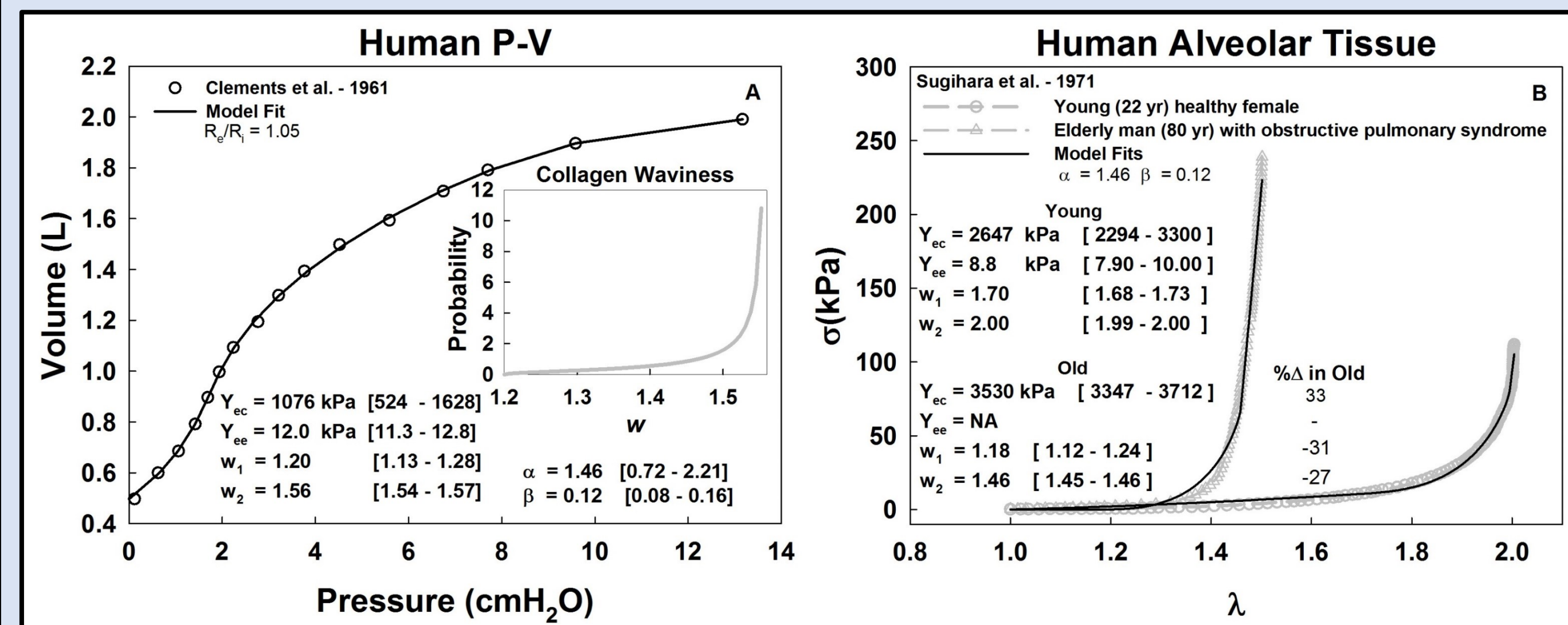
Results

Figure 1: Model fits to a P-V curve and alveolar strip data. A) The fit for a healthy human P-V curve with the six estimated model parameters and their confidence intervals. Inset: the estimated collagen waviness distribution. B) The fits for two alveolar strips using α and β obtained from A. **The parameters from the P-V and stress-strain curves are similar revealing a delayed recruitment of collagen fibers as well as indicating important age-related structural changes.**
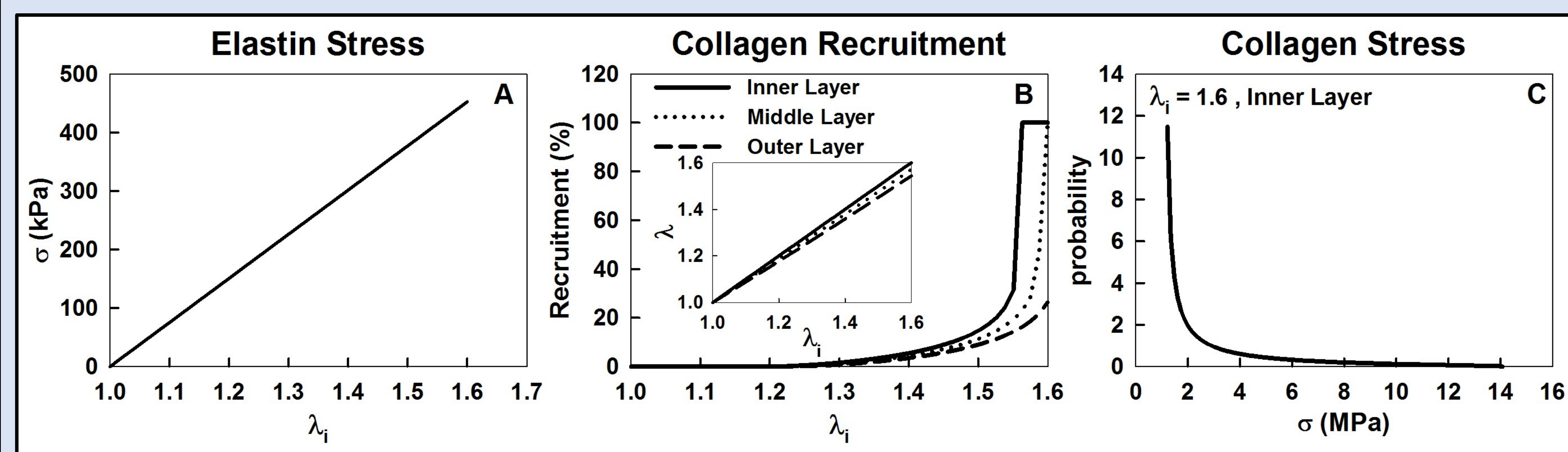

Figure 2: Single fiber analysis. A) Elastin fiber stress as a function of internal stretch ratio (λ_i). B) Collagen recruitment as a function of λ_i across the inner, middle and outer layer. Inset: λ at each layer as a function of λ_i. C) Collagen stress distribution for the inner layer at λ_i=1.6.
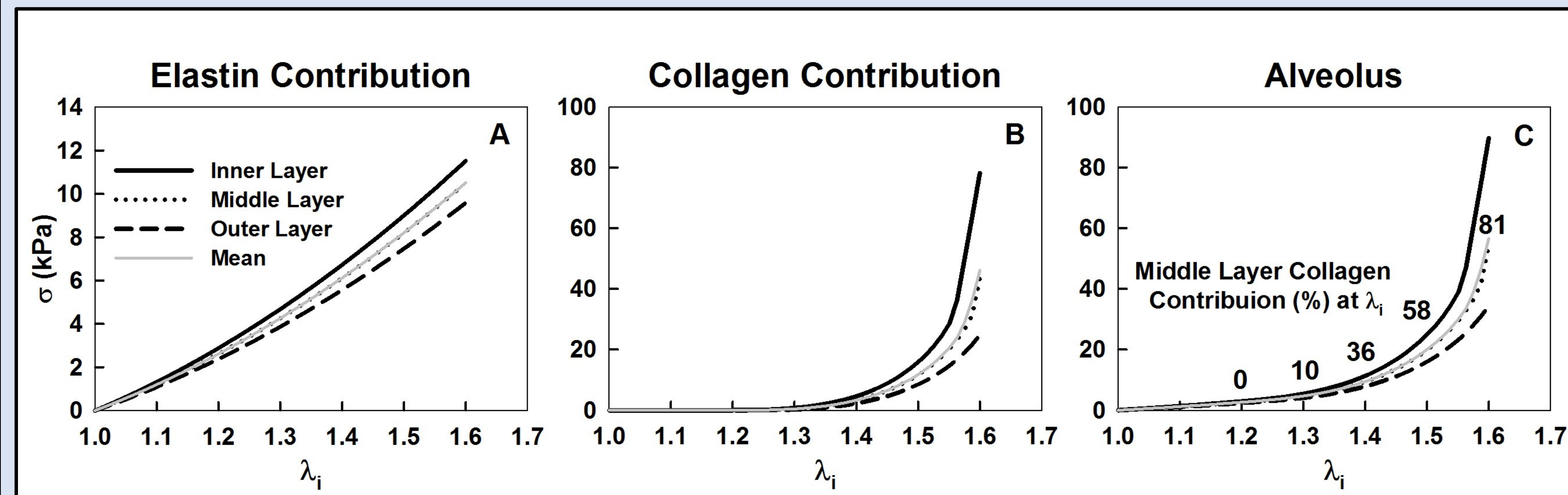

Figure 3: Alveolar stresses. A) σ_e B) σ_c and C) $\sigma_e + \sigma_c$ at three different layers (black lines) with the mean (gray line). Percent contribution of collagen from the total is shown in Fig. 3C at certain λ_is. **The analytically equated middle layer stress is equivalent to the numerically integrated mean stress.**
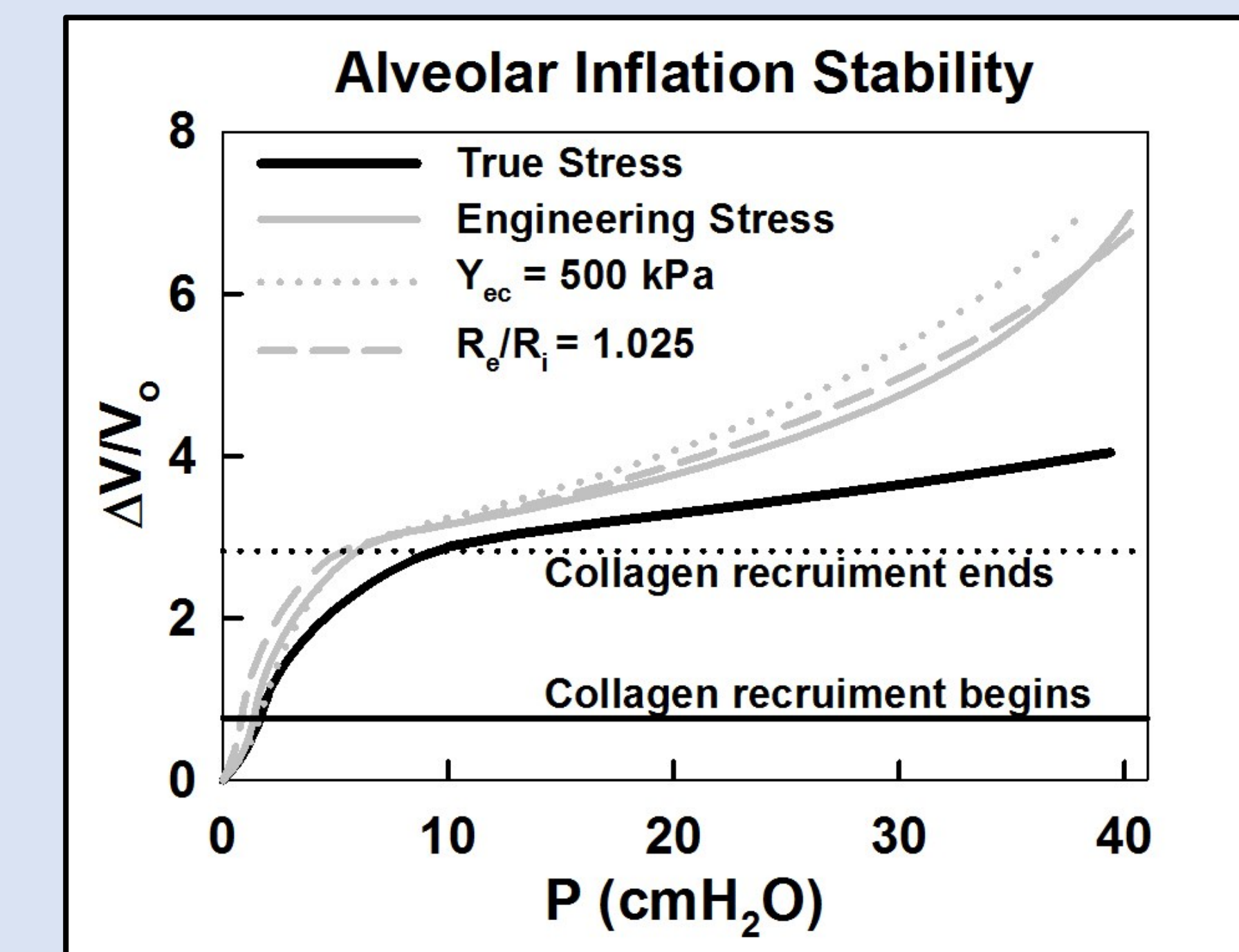

Figure 4: Alveolar inflation stability. P-V curves comparing true versus engineering stress, reduced collagen effective stiffness, and reduced R_e/R_i. **Inflation stability is due to the combined effects of mass conservation, collagen waviness and high stiffness, and alveolar thickness.**
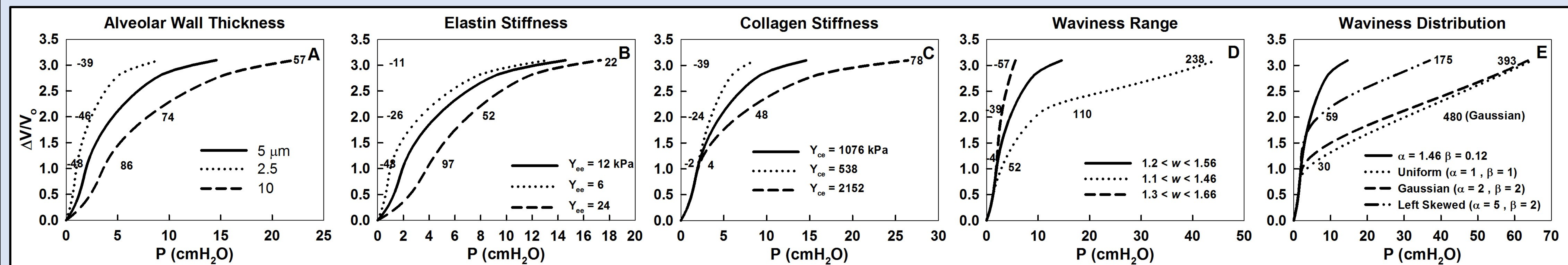

Figure 5: Sensitivity analysis. The effect on the P-V curve of A) wall thickness B) elastin stiffness, C) collagen stiffness, D) waviness range, and E) waviness distribution. Percentage differences based on the baseline simulation are indicated next to each curve for ΔV/Vo of 1, 2, and 3.

Conclusion

Modeling the behavior of elastin and collagen fibers inside the alveolar wall reveals the separate roles of each in the shape of the P-V curve and the stability of lung inflation. The model also provides estimates of the strains and stresses within the alveolar wall, which may by crucial for understanding how cells respond to mechanical cues, how tissue damage arises during mechanical ventilation, and how structural versus material alterations influence lung mechanics in disease.